```
FILE 'HOME' ENTERED AT 14:34:16 ON 03 DEC 2002

=> file medline, biosis, embase, scisearch, caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.42       0.42

FILE 'MEDLINE' ENTERED AT 14:35:17 ON 03 DEC 2002

FILE 'BIOSIS' ENTERED AT 14:35:17 ON 03 DEC 2002
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FILE 'CAPLUS' ENTERED AT 14:35:17 ON 03 DEC 2002
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=> s diabetes
L1      655376 DIABETES

=> s l1 and GIP promtoer
L2           0 L1 AND GIP PROMTOER

=> s l1 and GIP promoter
L3           6 L1 AND GIP PROMOTER

=> s l3 and insulin
L4           6 L3 AND INSULIN

=> s nucleic acid and insulin
L5        2777 NUCLEIC ACID AND INSULIN

=>

=> s l5 and GIP promoter
L6           0 L5 AND GIP PROMOTER

=> dup rem
ENTER L# LIST OR (END):l3
PROCESSING COMPLETED FOR L3
L7           2 DUP REM L3 (4 DUPLICATES REMOVED)

=> s l1 and secretagogue
L8         490 L1 AND SECRETAGOGUE

=> s l3 and GIP promoter
L9           6 L3 AND GIP PROMOTER

=> dup rem
ENTER L# LIST OR (END):l9
PROCESSING COMPLETED FOR L9
L10          2 DUP REM L9 (4 DUPLICATES REMOVED)
```

```
=> dup rem
ENTER L# LIST OR (END):l8
PROCESSING COMPLETED FOR L8
L11          226 DUP REM L8 (264 DUPLICATES REMOVED)

=> s l11 and py <= 2000
   2 FILES SEARCHED...
   4 FILES SEARCHED...
L12         179 L11 AND PY <= 2000

=> s l8 and insulin gene
L13           2 L8 AND INSULIN GENE
```

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PASSWORD:
 * * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'MEDLINE, BIOSIS, EMBASE, SCISEARCH, CAPLUS'
AT 15:19:01 ON 03 DEC 2002
FILE 'MEDLINE' ENTERED AT 15:19:01 ON 03 DEC 2002
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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    58.20      58.62

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -0.62      -0.62

=> s diabetes and gene therapy
L14       1726 DIABETES AND GENE THERAPY

=> s l14 and insulin gene
L15        210 L14 AND INSULIN GENE

=> dup rem
ENTER L# LIST OR (END):l15
PROCESSING COMPLETED FOR L15
L16         107 DUP REM L15 (103 DUPLICATES REMOVED)

=> s obesity
L17     213019 OBESITY

=> s l17 and gene therapy
L18        265 L17 AND GENE THERAPY

=> s l18 and leptin
L19         91 L18 AND LEPTIN

=> dup rem
ENTER L# LIST OR (END):l19
PROCESSING COMPLETED FOR L19
L20          64 DUP REM L19 (27 DUPLICATES REMOVED)

=> s l16 and py>= 1998
   3 FILES SEARCHED...
L21         70 L16 AND PY>= 1998

=> s l20 and py >= 1998
   4 FILES SEARCHED...
L22         58 L20 AND PY >= 1998
```

L7 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:876306 CAPLUS
DOCUMENT NUMBER: 134:51673
TITLE: Glucose-dependent insulin release from genetically engineered K cells
AUTHOR(S): Cheung, Anthony T.; Dayanandan, Bama; Lewis, Jamie T.; Korbutt, Gregory S.; Rajotte, Ray V.; Bryer-Ash, Michael; Boylan, Michael O.; Wolfe, M. Michael; Kieffer, Timothy J.
CORPORATE SOURCE: Departments of Medicine and Physiology, University of Alberta, Edmonton, AB, T6G 2S2, Can.
SOURCE: Science (Washington, D. C.) (2000), 290(5498), 1958-1962
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Genetic engineering of non-.beta.-cells to release insulin upon feeding could be a therapeutic modality for patients with **diabetes**. A tumor-derived K-cell line was induced to produce human insulin by providing the cells with the human insulin gene linked to the 5'-regulatory region of the gene encoding glucose-dependent insulinotropic polypeptide (GIP). Mice expressing this transgene produced human insulin specifically in gut K cells. This insulin protected the mice from developing **diabetes** and maintained glucose tolerance after destruction of the native insulin-producing .beta.-cells.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 179 MEDLINE

ACCESSION NUMBER: 2001177988 MEDLINE

DOCUMENT NUMBER: 21070626 PubMed ID: 11202569

TITLE: Development and characterization of pituitary GH3 cell clones stably transfected with a human proinsulin cDNA.

AUTHOR: Meoni C; Bertuzzi F; Pontiroli A E; Falqui L; Monaco L; Soria M; Arcelloni C; Paroni R; Foglieni C; Polastri L; Galbiati F; Folli F; Davalli A M

CORPORATE SOURCE: Cattedra di Clinica Medica, Universita Vita-Salute, H San Raffaele, Milan, Italy.

SOURCE: CELL TRANSPLANTATION, **(2000 Nov-Dec)** 9 (6) 829-40.
Journal code: 9208854. ISSN: 0963-6897.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200103

ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329

AB Successful beta-cell replacement therapy in insulin-dependent (type I) **diabetes** is hindered by the scarcity of human donor tissue and by the recurrence of autoimmune destruction of transplanted beta cells. Availability of non-beta cells, capable of releasing insulin and escaping autoimmune recognition, would therefore be important for **diabetes** cell therapy. We developed rat pituitary GH3 cells stably transfected with a furin-cleavable human proinsulin cDNA linked to the rat PRL promoter. Two clones (InsGH3/clone 1 and 7) were characterized in vitro with regard to basal and stimulated insulin release and proinsulin transgene expression. Mature insulin secretion was obtained in both clones, accounting for about 40% of total released (pro)insulin-like products. Immunocytochemistry of InsGH3 cells showed a cytoplasmic granular insulin staining that colocalized with secretogranin II (SGII) immunoreactivity. InsGH3 cells/clone 7 contained and released in vitro significantly more insulin than clone 1. **Secretagogue**-stimulated insulin secretion was observed in both InsGH3 clones either under static or dynamic conditions, indicating that insulin was targeted also to the regulated secretory pathway. Proinsulin mRNA levels were elevated in InsGH3 cells, being significantly higher than in betaTC3 cells. Moreover, proinsulin gene expression increased in response to various stimuli, thereby showing the regulation of the transfected gene at the transcriptional level. In conclusion, these data point to InsGH3 cells as a potential beta-cell surrogate even though additional engineering is required to instruct them to release insulin in response to physiologic stimulations.

L21 ANSWER 2 OF 70 MEDLINE
ACCESSION NUMBER: 2002613109 MEDLINE
DOCUMENT NUMBER: 22256473 PubMed ID: 12369716
TITLE: Prevention of **diabetes** in the NOD mouse by intra-muscular injection of recombinant adeno-associated virus containing the preproinsulin II gene.
AUTHOR: Jindal R M; Karanam M; Shah R
CORPORATE SOURCE: Department of Surgery, Indiana University School of Medicine, Indianapolis, USA.. r.jindalr@clinmed.gla.ac.uk
SOURCE: Int J Exp Diabetes Res, **(2001)** 2 (2) 129-38.
Journal code: 100962067. ISSN: 1560-4284.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20021010
Last Updated on STN: 20021031
Entered Medline: 20021030

AB Using the Adeno-associated virus (AAV) as a gene delivery vehicle, we have constructed a recombinant vector containing the full length rat preproinsulin gene (vLP-1). Utilizing the well described non-obese diabetic (NOD) mouse model, an experimental group (n = 10) of animals were intramuscularly (i.m.) injected with 10(7) rAAV virions containing the **insulin gene** and compared to a mock-injected control group (n = 10). Blood glucose (glc) was then measured weekly for 16 weeks. Data showed that the experimental group contained 70% euglycemic animals (defined as glc<200 mg/dL) versus 10% of the control animals (P < .05) at 14 weeks. Mean weight in the treated group was greater than the untreated group. Insulin mRNA was detected at the injection site of all of the treated animals, but not controls. Complete destruction of islets was confirmed by histology ruling out the possibility of spontaneous reversal of insulinitis. We conclude that i.m. delivery of the **insulin gene** in the NOD mouse was able to prevent clinical DM up to 14 weeks in a majority of treated animals. Our experimental data suggests that **gene therapy** may be an alternative treatment for IDDM in the future.

L21 ANSWER 4 OF 70 MEDLINE
ACCESSION NUMBER: 2002423689 IN-PROCESS
DOCUMENT NUMBER: 22167850 PubMed ID: 12180549
TITLE: Glucose-modulated transgene expression via recombinant adeno-associated virus.
AUTHOR: Yang Ya-Wun; Hsieh Yuan-Chiao; Chao Chih-Kai
CORPORATE SOURCE: School of Pharmacy, College of Medicine, National Taiwan University, Taipei.. ywyang@ha.mc.ntu.edu.tw
SOURCE: PHARMACEUTICAL RESEARCH, **(2002 Jul)** 19 (7) 968-75.
Journal code: 8406521. ISSN: 0724-8741.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020816
Last Updated on STN: 20020816

AB PURPOSE: The objective of this study was to examine glucose modulated reporter gene expression via recombinant adeno associated viral vectors both in vitro and in vivo. METHODS: Huh7 human hepatoma cells were transduced by recombi nant adeno-associated virus (rAAV) vectors containing the luciferase gene under control of the rat insulin I gene promoter and a cytomegalovirus immediate-early promoter driving-enhanced green fluores cence protein gene. The reporter gene expression was evaluated by glucose stimulation either in the absence or presence of insulin se cretagogues, including phorbol-12-myristate-13-acetate, dibutyryl cy clic AMP, and forskolin. In vivo studies were performed by injecting rAAV into the livers of streptozotocin-induced diabetic C57BL/6J mice followed by measurements of blood glucose concentration and luciferase activity assays 2 weeks after rAAV injection. RESULTS: At a multiplicity of infection of 500, approximately 66-69% of cells expressed enhanced green fluorescence protein at 48 h post transduction. Luciferase activities, driven by the **insulin gene** promoter, in the rAAV-transduced hepatoma cells responded to milli molars of glucose. The addition of phorbol-12-myristate-13-acetate dibutyryl cyclic AMP, and forskolin increased luciferase expression in the presence of either 1 mM or 25 mM glucose. The stimulation of luciferase activities by these substances was inhibited by the presence of 100 nM staurosporine. Exposure to increments of exogenous in sulin up to 10(-7) M inhibited luciferase gene expression in rAAV transduced Huh7 cells. The in vivo experiments demonstrated good correlation between luciferase activities and blood glucose levels in streptozotocin-induced diabetic animals. CONCLUSION: rAAV is a promising vector for hepatic **gene therapy** for **diabetes**. Glucose and insulin secretagogues modulated transgene ex pression in rAAV-transduced hepatoma cells, suggesting that condi tions affecting **insulin gene** promoter function in pancreatic islet beta cells also affect transgene expression in human hepatoma cells con ferred with **insulin gene** promoter. Results obtained from in viv experiments demonstrated that glucose modulated transgene expres sion can be obtained in rAAV-treated diabetic C57BL16J mice.

L21 ANSWER 9 OF 70 MEDLINE
ACCESSION NUMBER: 2002106747 MEDLINE
DOCUMENT NUMBER: 21674972 PubMed ID: 11815271
TITLE: Recent advances in **insulin gene therapy** for type 1 **diabetes**.
AUTHOR: Yoon Ji-Won; Jun Hee-Sook
CORPORATE SOURCE: Laboratory of Viral and Immunopathogenesis of Diabetes, Julia McFarlane Diabetes Research Center, Dept of Microbiology and Infectious Diseases, Faculty of Medicine, The University of Calgary, Calgary, Alberta, T2N 4N1, Canada.. yoon@ucalgary.ca
SOURCE: Trends Mol Med, **(2002 Feb)** 8 (2) 62-8. Ref: 62
Journal code: 100966035. ISSN: 1471-4914.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020213
Last Updated on STN: 20020326
Entered Medline: 20020325

AB Type 1 **diabetes** results from the loss of insulin-producing pancreatic beta cells following the action of beta-cell-specific autoimmune responses. One possible treatment for type 1 **diabetes** is the development of beta-cell substitutes by introducing an insulin-producing gene into non-beta cells, which would evade the beta-cell-specific autoimmune attack. However, this approach has been hampered by the absence of (1) an appropriate glucose-sensing system to regulate **insulin gene** transcription; (2) enzymes that process proinsulin to insulin; and (3) glucose-regulatable exocytosis in the target cells. Recent attempts to solve these problems have sought new methods for effective gene transfer and have addressed issues such as the expression and release of insulin in response to the physiological stimulus of glucose, the production of biologically active insulin, and the selection of an ideal target cell for the expression of the **insulin gene**.

L21 ANSWER 13 OF 70 MEDLINE
ACCESSION NUMBER: 2001383235 MEDLINE
DOCUMENT NUMBER: 21193101 PubMed ID: 11295563
TITLE: K cells: a novel target for **insulin gene therapy** for the prevention of **diabetes**.
AUTHOR: Corbett J A
CORPORATE SOURCE: The Edward A. Doisy Dept of Biochemistry and Molecular Biology, St Louis University School of Medicine, 1402 South Grand Blvd, St Louis, MO 63104, USA.. corbettj@slu.edu
SOURCE: TRENDS IN ENDOCRINOLOGY AND METABOLISM, **(2001 May-Jun)** 12 (4) 140-2. Ref: 20
Journal code: 9001516. ISSN: 1043-2760.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB Recently, gut K cells have been shown to express glucokinase, the glucose sensor of pancreatic beta cells, and transgenic mice expressing human insulin under the control of a K cell-specific promoter are resistant to **diabetes** development induced by the beta-cell toxin streptozotocin. These novel findings suggest that gut K cells might be a suitable target for gene therapeutic treatment of type 1 **diabetes** mellitus.

L21 ANSWER 20 OF 70 MEDLINE

ACCESSION NUMBER: 2001044886 MEDLINE
DOCUMENT NUMBER: 20534467 PubMed ID: 11083496
TITLE: Regulated hepatic **insulin gene therapy** of STZ-diabetic rats.
AUTHOR: Thule P M; Liu J M
CORPORATE SOURCE: Department of Medicine, Emory University School of Medicine, and Atlanta VA Medical Center, GA 30033, USA.
CONTRACT NUMBER: F32 DK08978 (NIDDK)
SOURCE: GENE THERAPY, **(2000 Oct)** 7 (20) 1744-52.
Journal code: 9421525. ISSN: 0969-7128.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001201

AB Effective and safe **insulin gene therapy** will require regulation of transgenic insulin secretion. We have created a liver-targeted insulin transgene by engineering glucose responsive elements into a hepatic promoter containing an inhibitory insulin response sequence. In this work, we demonstrate application of this transgene for the treatment of **diabetes** mellitus in vivo, by administering a recombinant adenovirus vector, Ad/(GIRE)3BP-1 2xfur, to rats made diabetic with streptozotocin. We verified hepatic expression of transgenic insulin by RT-PCR, and confirmed glucose responsive stimulation of transgenic insulin secretion in vivo by serum RIA. Following a portal system injection of either Ad/(GIRE)3BP-1 2xfur, or an empty adenoviral vector, animals made diabetic with either low (120 mg/kg), or high (290 mg/kg) dose streptozotocin (STZ) were monitored for changes in body weight, and blood glucose. Without subcutaneous insulin injections, blood glucose values of sham-treated animals (n = 8) remained elevated, and animals failed to gain weight (n = 4), or died (n = 4). In contrast, body weight of Ad/(GIRE)3BP-1 2xfur-treated animals (n = 13) increased, and blood glucose remained at near normal levels from one to 12 weeks. Glucose values <50 mg/dl were infrequently observed, and no Ad/(GIRE)3BP-1 2xfur-treated animal succumbed to hypoglycemia. Treatment with the insulin transgene enabled diabetic animals to reduce blood sugars following a glucose load, and to maintain blood sugar levels during a 10-h fast. Hepatic production of human insulin produced near normal glycemia, and weight gain, without exogenous insulin, and without lethal hypoglycemia. In conclusion, we have demonstrated the feasibility of utilizing transcription to control transgenic insulin production in a rodent model of **diabetes** mellitus

L21 ANSWER 25 OF 70 MEDLINE
ACCESSION NUMBER: 2000036953 MEDLINE
DOCUMENT NUMBER: 20036953 PubMed ID: 10567666
TITLE: Present and potential future use of **gene therapy** for the treatment of non-insulin dependent **diabetes** mellitus (Review).
AUTHOR: Freeman D J; Leclerc I; Rutter G A
CORPORATE SOURCE: Department of Biochemistry, School of Medical Sciences, University Walk, University of Bristol, Bristol BS8 1TD, UK.
SOURCE: INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE, **(1999 Dec)** 4 (6) 585-92. Ref: 62
Journal code: 9810955. ISSN: 1107-3756.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000124
Last Updated on STN: 20000124
Entered Medline: 20000110

AB This review describes the latest approaches towards using **gene therapy** as a treatment for non-insulin dependent **diabetes** mellitus (NIDDM; Type 2 **diabetes**). We examine attempts to directly deliver the **insulin gene** to non-beta-cells, to improve insulin secretion from existing beta-cells and to develop ex vivo approaches to implanting genetically modified cells. Future research into the pathology of non-insulin dependent **diabetes**, combined with the latest developments in gene delivery systems, may potentially make **gene therapy** an attractive alternative NIDDM treatment in the future.